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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/674,090	EICHEN ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2010 and 08 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,18-20,22-26,28,35-39,41,43,44,47-51,53-57,60-63 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9,18-20,22-26,28,35-39,41,43,44,47-51,53-57,60-63 and 65* is/are rejected.

7)☒ Claim(s) *19,35 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/10*.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's responses filed on July 12, 2010 and November 8, 2010 are acknowledged. Claims 1, 4-9, 18-20, 22-26, 28, 35-39, 41, 43, 44, 47-51, 53-57, 60-63, and 65 are currently pending. In the response, Applicant amended claims 1, 19, 20, 22-26, 28, 35, 37-39, 43, 44, 49-51, and 65.

The following include new grounds of rejection necessitated in part by Applicant's amendments to the claims. Any previously made rejections or objections not reiterated below have been withdrawn. Applicant's arguments filed on July 12, 2010 have been fully considered and are discussed in the "Response to Arguments" section. Since not all of the new grounds of rejection below were necessitated by Applicant's amendment, this office action is **NON-FINAL**.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on November 19, 2010 is acknowledged. A signed copy is enclosed.

Drawings

3. Applicant's submission of replacement drawing sheets on July 12, 2010 is acknowledged. The replacement drawings are acceptable.

Claim Interpretation

4. The recitation "means for determining whether the one or more targets are in the sample as a result of the extent of electric conductance between the two electrodes of each assay set", which appears in claims 35 and 37, has been treated under 35 U.S.C. 112, sixth paragraph.

Claim Objections

5. Claim 19 is objected to because of the following informalities: The recitation "the respective recognition moiety in each respective assay set is capable of specific binding to a type of the target component is the same" is grammatically incorrect.

Claim 35 is objected to because of the following informalities: This claim appears to be missing the words "which are" after "targets" in line 14.

Claim 49 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 49 is drawn to the method of claim 24 and recites that the biological molecule targets are selected from a bacterium, virus, or cell. Claim 24 recites that the biological molecule targets are nucleic acids, and, therefore, claim 49 fails to limit the method of claim 24, since not all of the elements of independent claim 24 are still present in dependent claim 49.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28, 43, 44, 49, 51, 53-56, and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28 and 65 are indefinite, because there is insufficient antecedent basis for "the at least two respective electrodes", which is recited in line 5 of claim 28 and in part (c), lines 10-11 of claim 65.

Claims 43 and 44 are drawn to the system of claim 1, wherein the target component of the target bacterium, virus, or cell is a nucleic acid, and the recognition moiety is an oligonucleotide that is complementary to said nucleic acid. Claims 53 and 54 are drawn to the devices of claim 35 and 37, respectively, wherein the recognition moiety is a nucleic acid molecule. Claims 1, 35, and 37 require the system or device to be capable of detecting a complex formed as a result of the following interactions: (i) specific binding of a recognition moiety to a target component of a cell, bacterium, or virus and (ii) non-specific binding of a nucleation center-forming entity to the cell, bacterium, or virus. The formation of such a complex requires the target component to be present on the surface of the cell, bacterium, or virus. Since nucleic acids are not found on the surface of cells or viruses, it is unclear how the target component and recognition moiety can be a nucleic acid and an oligonucleotide, respectively. As a result, claims 43, 44, 53, and 54 are vague and indefinite.

Claim 49 is drawn to the method of claim 24, wherein the target is a bacterium, virus, or cell. Since claim 24 requires that the target is a nucleic acid, it is not clear how the target can also be a cell as required by claim 49. Also, since nucleic acids are not found on the surface of cells or viruses, it is unclear how the cellular or viral target could bind to the oligonucleotide recognition moiety recited in claim 24 as required by claim 49. Accordingly, claim 49 is indefinite.

Claim 51 is indefinite, because the requirements of the claim are unclear. Claim 51 is drawn to the method of claim 26 and requires the target to be a bacterium, a cell, or a virus. It is not clear how these target options can function in the method of claim 26, because the use of monomers of a conductive polymer in the method of claim 26 would appear to limit the targets to nucleic acid molecules into which nucleotide monomers could be incorporated. It is not clear, therefore, whether claim 51 is missing essential elements or method steps, if the claim was intended to depend from another claim, or if the word "component" was not intended to be deleted after the words "bacterium", "cell", and "virus". Accordingly, claim 51 is vague and indefinite.

Claims 55 and 56 are indefinite, because there is insufficient antecedent basis for "said means", which is recited in line 2 of these claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS) and further in view of Hurley et al. (Methods in Enzymology (1990) 184: 429-433; newly cited).

These claims are drawn to a system for detecting the presence of a target selected from the group consisting of a bacterium, a cell, or a virus in a sample that comprises a substrate upon which two electrodes are attached, a recognition moiety that binds to a component of the target immobilized on the substrate between the electrodes, and nucleation center-forming entities that bind non-specifically to the target.

Mroczkowski teaches methods and systems for detecting the presence of targets in a sample based on the measurement of an electrical signal generated between two electrodes (see abstract, Figures 1-2, and page 3, lines 2-27).

Regarding claims 1, 57, and 65, Mroczkowski teaches a system for detecting the presence of one or more targets in a sample that comprises:

(a) an assay device having one or more assay sets, wherein each of the assay sets comprises at least two electrodes positioned on a substrate and separated by a gap and a recognition moiety, that is capable of specifically binding to a component of one of the one or more targets, positioned in the gap, and bound to the substrate (see page 10, lines 7-12 and lines 24-29; see also page 3, lines 1-37, page 12, lines 1-23, page 17, lines 4-32, and Figures 1, 2, and 8, which provides further details regarding the "diagnostic element" referenced at page 10 of Mroczkowski, which corresponds to the claimed assay device having one or more assay sets),

(b) an electric or electronic module arranged and configured to measure electric conductance between the at least two electrodes of the one or more assay sets (see page 17, line 33 - page 18, line 8 and page 23, where the ohmmeter measures electric conductance (i.e. reciprocal ohms) indirectly via the measurement of ohms of resistance),

(c) a sample that may or may not contain the target (page 10, lines 7-18 and lines 24-36),

(d) reagents comprising nucleation center-forming entities that bind to a component of the one or more biological targets (see page 10, lines 7-18 and page 10, lines 24-36, where the conductively-labeled antibodies are the nucleation center-forming entities; page 14, lines 3-12, page 18, lines 28-31, and page 20, lines 11-33, for example, teach that the conductive label may be gold particles, which are a nucleation center-forming entity),

(e) reagents comprising metal ions and a reducing agent (see page 10, lines 7-23 and page 10, line 24 - page 11, line 5; see also page 15, lines 9-19, page 18, lines 21-31, where

Mroczkowski teaches silver enhancement of gold particles, such as gold-conjugated antibodies; page 25, lines 13-29 provides further details of the silver enhancement process), and

(f) means for determining whether at least one of the one or more targets are in the sample as a result of the extent of electric conductance between the two electrodes in each assay set (see page 17, line 33 - page 18, line 8 and page 23, where the ohmmeter, which measures electric conductance (i.e. reciprocal ohms) indirectly via the measurement of ohms of resistance, constitutes the claimed means).

Further regarding claims 1 and 65, the system of Mroczkowski is adapted to allow combination of the one or more assay sets, the sample, and the reagents. Also, in use, the recognition moieties in the system of Mroczkowski bind to a component of the target to form a complex that is bound by the nucleation center-forming entities (see above, especially page 10). As noted above (see pages 18 and 25), the complex formation step is followed by a silver enhancement step in which the metal ions and reducing agent are used to deposit silver upon the nucleation center-forming entities (i.e. the gold particles) to form a conductive silver bridge between each pair of electrodes. Further, as evidenced by the specification of the instant application at page 42, the acidic solution of silver ions and hydroquinone taught by Mroczkowski at page 25, lines 13-29, for example, is metastable, which results in metal deposition only occurring when a nucleation center-forming entity is present.

Further regarding claim 65, Mroczkowski also teaches that the recognition moiety, which may be an antibody capable of specifically binding to an epitope of a cellular target can be attached to each of the two electrodes (page 12, lines 1-11, page 14, lines 3-15, and page 10, lines 7-23).

Regarding claims 4 and 6, Mroczkowski teaches that the nucleation center-forming entities are colloidal gold particles (see page 20, for example).

Regarding claims 5 and 7, Mroczkowski teaches that the nucleation center-forming entities are metal complexes, specifically gold complexes or platinum complexes (see, for example, page 14, lines 26-30).

Regarding claims 18-20, the system of Mroczkowski comprises a plurality of assay sets (see Figure 8 and page 17, lines 4-32). Mroczkowski further teaches that the recognition moiety in each assay set may be the same or different between assay sites to permit binding to the same or different targets (page 17, lines 8-12).

Regarding claims 22 and 23, Mroczkowski teaches that the component of the target bound by the recognition moiety is a protein or polypeptide, and that the recognition moiety is an antibody (see, for example, page 10, lines 7-22, for example).

Mroczkowski does not teach that the nucleation center-forming entities bind non-specifically to cells, bacteria, or viruses, as required by independent claims 1 and 65. Mroczkowski also does not teach the use of a computer as the means for determining the presence of the target in the sample as required by claims 55 and 65.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see abstract, Figure 4, Figure 22, and column 2, lines 25-52).

Regarding claims 1, 57, and 65, the system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition

moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37, column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22).

Further regarding claim 1 and also regarding claims 43 and 44, Hollis teaches that the target biological molecule detected using the disclosed system and methods may be a cell, protein, or nucleic acid (see column 4, lines 21-25 and lines 41-45 and Table III at column 18). The nucleic acids detected by Hollis include nucleic acids that are a component of a cell or virus (see, for example, column 16, line 35 - column 17, line 67). Hollis teaches that the detection of nucleic acid targets can be used in applications such as "genetic research, genetic and infectious disease diagnosis, toxicology testing, individual identification, agriculture identification and breed optimization, quality assurance through contaminant detection, and occupational hazard screening via mutation detection (column 16, lines 35-42)." Also, in the embodiments comprising cell or nucleic acid detection, Hollis teaches that the recognition moiety is a molecule, such as a protein or antibody that binds to a component of the cell or a complementary oligonucleotide, respectively (see, for example, Table III at column 18). In Table III at column 18, Hollis also teaches the use of biotin-avidin interactions to detect targets of interest.

Further regarding claim 65 and also regarding claim 55, Hollis teaches that "[T]he measurement process can be automated via on-chip microprocessor control to provide a very fast method of accessing each test site in the array" (column 20, lines 14-16).

Regarding claims 18-20, the system of Hollis comprises a plurality of assay sets (column 4, lines 15-49, for example). Hollis further teaches that the recognition moiety in each assay set may be capable of binding to the same type of cell component and also that the recognition moieties differ between assay sets to permit binding to different targets (see column 4, lines 36-49, for example).

Regarding claims 22 and 23, Hollis teaches that the component of the target bound by the recognition moiety is a protein or polypeptide, and that the recognition moiety is an antibody (see, for example, Table III at column 18).

Hollis does not teach non-specific binding of nucleation center forming entities to a target selected from a bacterium, a virus, or a cell as required by the instant claims.

Hurley teaches that cells can be labeled with biotin to permit subsequent detection with a labeled streptavidin molecule (pages 429-430). Hurley teaches that the use of the biotin-streptavidin system eliminates the need to design specific antibodies for different cell surface proteins (page 429).

Hurley does not teach labeling the streptavidin with a nucleation center forming entity.

Olsen teaches that streptavidin may be conjugated to colloidal gold to permit detection of biotin-labeled targets of interest in a sample (column 4, lines 42-67). Olsen also teaches that the disclosed streptavidin-conjugated gold particles may be used in an assay comprising specific capture of a biotin-labeled target of interest using an immobilized recognition moiety followed

by detection of the resulting complexes using the streptavidin-conjugated gold particles (column 2, lines 32-61 and column 3, lines 48-62).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Hollis, Olsen, and Hurley with those of Mroczkowski. An ordinary artisan would have been motivated by the teachings of Hollis to adapt the systems, devices, and methods of Mroczkowski to the detection of any biological target, such as cells or nucleic acids, in order to maximize the number of useful applications of the method. Since Hollis taught that nucleic acid detection and cell detection could be used in numerous useful applications (column 16, lines 35-42 and column 19, lines 5-15), an ordinary artisan would have been motivated to adapt the device of Mroczkowski to the detection of these useful biological targets in order to further increase the number of useful applications of the system. An ordinary artisan would have had a reasonable expectation of success in doing so, since Mroczkowski taught that the method was not limited to any particular target and since Hollis taught that cells and nucleic acids were suitable targets for detection via electrical methods.

It also would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate a computer as the means for determining the presence of a target in a sample in the systems and devices of Mroczkowski. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Hollis taught that the electrical measurements in a similar system could be conducted using a computer to result in a rapid and automated detection step (column 20, lines 14-16).

Finally, it would have been obvious for the ordinary artisan practicing the methods suggested by the combined teachings of Mroczkowski and Hollis to label the target cells with

biotin as taught by Hurley to permit detection with streptavidin-conjugated gold particles as taught by Olsen. Since Hurley taught that cells could be labeled with biotin to permit non-specific detection with labeled streptavidin and avoid the need for specific labeled antibodies (e.g., the labeled antibodies described by Mroczkowski), the ordinary artisan would have recognized that non-specific detection via biotin-streptavidin would reduce the cost associated with practicing the methods of Mroczkowski. The ordinary artisan would have had a reasonable expectation of success in doing so, since Hurley taught that the biotin-labeling step did not inhibit binding of the cell surface proteins to antibodies (page 433), and Olsen taught that streptavidin-conjugated gold particles could be used to detect virtually any biotinylated target of interest in a sandwich assay (see above).

Thus, the systems of claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65 are prima facie obvious in view of the combined teachings of the cited references.

9. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS) and further in view of Hurley et al. (Methods in Enzymology (1990) 184: 429-433; newly cited) and further in view of Kidwell et al. (US 5,384,265; cited previously) and further in view of Houthoff et al (US 5,985,566; cited previously).

Claim 8 is drawn to the system of claim 4, wherein the colloid particles that comprise the nucleation center-forming entity are colloidal platinum particles. Claim 9 is drawn to the system of claim 5, wherein the nucleation center-forming entities are platinum complexes or clusters.

As discussed above, the combined teachings of Mroczkowski, Hollis, Olsen, and Hurley render obvious the system of claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65.

Mroczkowski teaches the use of colloidal gold particles (page 20, for example) and also platinum complexes may be used as the nucleation center-forming entity (see page 14, lines 26-30 and page 20, for example).

However, neither Mroczkowski nor Hollis teaches the use of colloidal platinum as the nucleation center-forming entity as required by claim 8. Also, neither Mroczkowski nor Hollis teaches that the platinum complexes can be subjected to silver enhancement.

Hurley and Olsen do not remedy this deficiency in Mroczkowski and Hollis.

Kidwell teaches that colloidal platinum may be used in a manner analogous to colloidal gold to immobilize proteins that bind to a target molecule present in a sample (column 4, lines 45-57 and column 7, lines 1-67).

Kidwell does not teach subjecting the colloidal platinum particles to silver enhancement.

Houthoff teaches that platinum may be conjugated (complexed) to biological molecules, such as proteins and nucleic acids, and used to detect the presence of a target molecule that binds to the platinum-immobilized biological molecule (column 2, lines 25-57 and column 4, lines 22-52). Houthoff further teaches that the platinum complexes of the invention can be used as a nucleation site for detection via silver enhancement using silver ions and a reducing agent, such as hydroquinone (column 12, line 66 – column 13, line 3 and column 24, line 64 – column 25, line 17).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize colloidal platinum or platinum complexes as the nucleation center-forming

entities in the system resulting from the combined teachings of Mroczkowski, Hollis, Olsen, and Hurley. As noted in MPEP 2144.06, the substitution of art-recognized equivalents known to be useful for the same purpose is prima facie obvious in the absence of unexpected results. In this case, as evidenced by the teachings of Kidwell and Houthoff, colloidal platinum and platinum complexes could be conjugated to biological molecules, such as proteins and nucleic acids, and used in methods of detecting target biological molecules comprising silver enhancement that were analogous to the methods comprising the use of antibody-conjugated gold particles taught by Mroczkowski and streptavidin-conjugated gold particles taught by Olsen. Also, no evidence of unexpected results with respect to the use of platinum as the nucleation center-forming entity has been presented. Accordingly, an ordinary artisan would have been motivated to select this art-recognized equivalent for incorporation in the system resulting from the combined teachings of Mroczkowski, Hollis, Olsen, and Hurley with a reasonable expectation of success. Thus, the systems of claims 8 and 9 are prima facie obvious in view of the combined teachings of the cited references.

10. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS).

These claims are drawn to methods and a device for detecting the presence of one or more targets in a sample based on an observed change in electric conductance resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes.

Mroczkowski teaches methods and devices for detecting the presence of targets in a sample based on the measurement of an electrical signal generated between two electrodes (see abstract, Figures 1-2, and page 3, lines 2-27).

Regarding claim 24, Mroczkowski teaches a method for detecting the presence of one or more biological molecule targets in a sample comprising:

(a) providing an assay device having one or more assay sets, wherein each of the assay sets comprises at least two electrodes positioned on a substrate and separated by a gap and a recognition moiety that is capable of specifically binding to one of the one or more biological molecule targets, positioned in the gap, and bound to the substrate (see page 10, lines 7-12 and lines 24-29; see also page 3, lines 1-37, page 12, lines 1-23, page 17, lines 4-32, and Figures 1, 2, and 8, which provides further details regarding the "diagnostic element" referenced at page 10 of Mroczkowski, which corresponds to the claimed assay device having one or more assay sets),

(b) contacting the assay device with the sample under conditions that permit the formation of complexes between the biological molecule target and the recognition moiety (page 10, lines 7-18 and lines 24-36),

(c) contacting the assay device with a first reagent solution to bind nucleation center-forming entities to the one or more biological targets complexed with the recognition moiety (see page 10, lines 7-18 and page 10, lines 24-36, where the conductively-labeled antibodies are the nucleation center-forming entities; page 14, lines 3-12, page 18, lines 28-31, and page 20, lines 11-33, for example, teach that the conductive label may be gold particles, which are a nucleation center-forming entity),

(d) contacting the assay device with a second reagent that includes metal ions and a reducing agent to deposit metal on the complexes formed in step (c) if one or more of the nucleation center-forming entities is present, whereby the deposited metal forms a conducting metal layer over the nucleation center-forming entities and a conductive bridge between the two electrodes (see page 10, lines 7-23 and page 10, line 24 - page 11, line 5; see also page 15, lines 9-19, page 18, lines 21-31, where Mroczkowski teaches silver enhancement of gold particles, such as gold-conjugated antibodies; page 25, lines 13-29 provides further details of the silver enhancement process), and

(e) connecting the electrodes to an electric or electronic module and measuring the conductance between the two electrodes, wherein a conductance measurement above a threshold conductance value indicates the presence of a biological molecule target in the sample, whereas a conductance measurement below or at the threshold conductance value indicates the absence of the biological molecule target in the sample (see page 10, lines 7-23 and page 10, line 24 – page 11, line 5, where the resistance measurements conducted with an ohmmeter provide an indirect measure of the conductance, which is reciprocal ohms; see also page 17, line 33 - page 18, line 8, and page 23 for additional details of the resistance measurements conducted by Mroczkowski).

Further regarding claim 24, as evidenced by the specification of the instant application at page 42, the acidic solution of silver ions and hydroquinone taught by Mroczkowski at page 25, lines 13-29, for example, is metastable, which results in metal deposition only occurring when a nucleation center-forming entity is present.

Mroczkowski does not teach applying the disclosed methods to the detection of nucleic acid targets using oligonucleotide recognition moieties as required by claim 24. Mroczkowski

also does not teach non-specific deposition of the nucleation center forming entities onto the target.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see abstract, Figure 4, Figure 22, column 2, lines 25-52, column 4, lines 21-25, column 4, lines 41-45, and Table III at column 18). The system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37, column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22). Hollis teaches that the detection of nucleic acid targets can be used in applications such as "genetic research, genetic and infectious disease diagnosis, toxicology testing, individual identification, agriculture identification and breed optimization, quality assurance through contaminant detection, and occupational hazard screening via mutation detection (column 16, lines 35-42)." Also, in the embodiments comprising nucleic acid detection, Hollis teaches that the recognition moiety is a complementary oligonucleotide (see Table III at column 18). In Table III at column 18, Hollis also teaches the use of biotin-avidin interactions to detect targets of interest.

Hollis does not teach non-specific binding of nucleation center forming entities to a nucleic acid target as required by the instant claims.

Olsen teaches that streptavidin may be conjugated to colloidal gold to permit detection of biotin-labeled targets of interest in a sample (column 4, lines 42-67). Olsen also teaches that the disclosed streptavidin-conjugated gold particles may be used in an assay comprising specific capture of a biotin-labeled target of interest using an immobilized recognition moiety followed by detection of the resulting complexes using the streptavidin-conjugated gold particles (column 2, lines 32-61 and column 3, lines 48-62).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Hollis and Olsen with those of Mroczkowski. An ordinary artisan would have been motivated by the teachings of Hollis to adapt the systems, devices, and methods of Mroczkowski to the detection of any biological target, such as nucleic acids, in order to maximize the number of useful applications of the method. Since Hollis taught that nucleic acid detection could be used in numerous useful applications (column 16, lines 35-42 and column 19, lines 5-15), an ordinary artisan would have been motivated to adapt the method of Mroczkowski to the detection of these useful biological targets in order to further increase the number of useful applications. An ordinary artisan would have had a reasonable expectation of success in doing so, since Mroczkowski taught that the method was not limited to any particular target, and Hollis taught that nucleic acids were suitable targets for electrical detection.

It also would have been prima facie obvious for the ordinary artisan practicing the methods suggested by the combined teachings of Mroczkowski and Hollis to label the target nucleic acids with biotin as taught by Olsen to permit detection with streptavidin-conjugated

gold particles as taught by Olsen. Since Olsen taught that nucleic acids could be labeled with biotin to permit non-specific detection with labeled streptavidin, the ordinary artisan would have recognized that non-specific detection via biotin-streptavidin would reduce the cost associated with practicing the methods of Mroczkowski. The ordinary artisan would have had a reasonable expectation of success in doing so, since Olsen taught that streptavidin-conjugated gold particles could be used to detect virtually any biotinylated target of interest in a sandwich assay (see above). Thus, the method of claim 24 is prima facie obvious in view of the combined teachings of the cited references.

11. Claims 25 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Olsen et al. (US 5,556,756; cited on an IDS).

These claims are drawn to methods for detecting the presence of one or more targets, specifically nucleic acids, in a sample based on an observed change in electric conductance resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes.

Mroczkowski teaches methods and devices for detecting the presence of targets in a sample based on the measurement of an electrical signal generated between two electrodes (see abstract, Figures 1-2, and page 3, lines 2-27).

Regarding claim 25, Mroczkowski teaches a method for detecting the presence of one or more biological molecule targets in a sample comprising:

(a) reacting a sample, which may or may not have at least one of the biological molecule targets with a first reagent solution to bind nucleation center-forming entities to the one or more biological targets (see page 10, lines 24-36, where the conductively-labeled anti-IgG or anti-IgE antibodies are nucleation center-forming entities that bind semi-specifically to the antigen-captured antibody targets; see also page 14, lines 3-12, page 18, lines 28-31, and page 20, lines 11-33, where Mroczkowski teaches that the conductive label may be gold particles),

(b) providing an assay device having one or more assay sets, wherein each of the assay sets comprises at least two electrodes positioned on a substrate and separated by a gap and a recognition moiety that is capable of specifically binding to one of the one or more biological molecule targets, positioned in the gap, and bound to the substrate (see page 10, lines 24-29; see also page 3, lines 1-37, page 12, lines 1-23, page 17, lines 4-32, and Figures 1, 2, and 8, which provides further details regarding the "diagnostic element" referenced at page 10 of Mroczkowski, which corresponds to the claimed assay device having one or more assay sets),

(c) contacting the assay device with the sample under conditions that permit the formation of complexes between the biological molecule target and the recognition moiety (page 10, lines 24-36),

(d) contacting the assay device with a second reagent that includes metal ions and a reducing agent to deposit metal on the complexes formed in step (c) if one or more of the nucleation center-forming entities is present, whereby the deposited metal forms a conducting metal layer over the nucleation center-forming entities and a conductive bridge between the two electrodes (see page 10, line 24 - page 11, line 5; see also page 15, lines 9-19, page 18, lines 21-31, where Mroczkowski teaches silver enhancement of gold particles, such as gold-conjugated

antibodies; see also page 25, lines 13-29, which provides further details of the silver enhancement process),

(e) connecting the electrodes to an electric or electronic module and measuring the conductance between the two electrodes, wherein a conductance measurement above a threshold conductance value indicates the presence of a biological molecule target in the sample, whereas a conductance measurement below or at the threshold conductance value indicates the absence of the biological molecule target in the sample (see page 10, line 24 – page 11, line 5, where the resistance measurements conducted with an ohmmeter provide an indirect measure of the conductance, which is reciprocal ohms; see also page 17, line 33 - page 18, line 8, and page 23 for additional details of the resistance measurements conducted by Mroczkowski).

Further regarding claim 25, as evidenced by the specification of the instant application at page 42, the acidic solution of silver ions and hydroquinone taught by Mroczkowski at page 25, lines 13-29, for example, is metastable, which results in metal deposition only occurring when a nucleation center-forming entity is present.

Mroczkowski does not teach non-specific deposition of the nucleation center forming entities onto the target. Mroczkowski also does not teach that the target biological molecule is a nucleic acid and the recognition moiety is an oligonucleotide as required by claim 47.

Olsen teaches that streptavidin may be conjugated to colloidal gold to permit detection of biotin-labeled targets of interest in a sample, such as nucleic acids (column 4, lines 42-67). Olsen also teaches that the disclosed streptavidin-conjugated gold particles may be used in an assay comprising specific capture of a biotin-labeled target of interest, such as a nucleic acid, using an immobilized recognition moiety, such as an oligonucleotide, followed by detection of

the resulting complexes using the streptavidin-conjugated gold particles (column 2, lines 32-61 and column 3, lines 48-62).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Olsen with those of Mroczkowski. An ordinary artisan would have been motivated to label the target biological molecule with biotin as taught by Olsen to permit detection with streptavidin-conjugated gold particles as taught by Olsen. Since Olsen taught that nucleic acids or proteins could be labeled with biotin to permit non-specific detection with labeled streptavidin, the ordinary artisan would have recognized that non-specific detection via biotin-streptavidin would reduce the cost associated with practicing the methods of Mroczkowski. An ordinary artisan also would have been motivated by the teachings of Olsen to apply the method of Mroczkowski to the detection of any desired biological target molecule, such as nucleic acids, in order to increase the number of useful applications of the technology. The ordinary artisan would have had a reasonable expectation of success in doing so, since Olsen taught that streptavidin-conjugated gold particles could be used to detect virtually any biotinylated target of interest in a sandwich assay similar to the assay of Mroczkowski (see above). Thus, the methods of claims 25 and 47 are prima facie obvious in view of the combined teachings of the cited references.

12. Claims 26, 28, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS) and further in view of Engelhardt et al. (US 5,241,060; cited on an IDS).

These claims are drawn to methods and a device for detecting the presence of one or more targets in a sample based on an observed change in electric conductance resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes.

Mroczkowski teaches methods and devices for detecting the presence of targets in a sample based on the measurement of an electrical signal generated between two electrodes (see abstract, Figures 1-2, and page 3, lines 2-27).

Regarding claims 26 and 28, Mroczkowski teaches a method for detecting the presence of one or more biological molecule targets in a sample comprising:

(a) providing an assay device having one or more assay sets, wherein each of the assay sets comprises at least two electrodes positioned on a substrate and separated by a gap and a recognition moiety that is capable of specifically binding to one of the one or more biological molecule targets, positioned in the gap, and bound to the substrate (see page 10, lines 7-12 and lines 24-29; see also page 3, lines 1-37, page 12, lines 1-23, page 17, lines 4-32, and Figures 1, 2, and 8, which provides further details regarding the "diagnostic element" referenced at page 10 of Mroczkowski, which corresponds to the claimed assay device having one or more assay sets),

(b) contacting the assay device with the sample under conditions that permit the formation of complexes between the biological molecule target and the recognition moiety (page 10, lines 7-18 and lines 24-36),

(c) contacting the assay device with a first reagent solution to bind nucleation center-forming entities to the one or more biological targets complexed with the recognition moiety (see page 10, lines 7-18 and page 10, lines 24-36, where the conductively-labeled antibodies are the nucleation center-forming entities; page 14, lines 3-12, page 18, lines 28-31, and page 20, lines

11-33, for example, teach that the conductive label may be gold particles, which are a nucleation center-forming entity),

(d) contacting the assay device with a second reagent that includes metal ions and a reducing agent to deposit metal on the complexes formed in step (c) if one or more of the nucleation center-forming entities is present, whereby the deposited metal forms a conducting metal layer over the nucleation center-forming entities and a conductive bridge between the two electrodes (see page 10, lines 7-23 and page 10, line 24 - page 11, line 5; see also page 15, lines 9-19, page 18, lines 21-31, where Mroczkowski teaches silver enhancement of gold particles, such as gold-conjugated antibodies; page 25, lines 13-29 provides further details of the silver enhancement process), and

(e) connecting the electrodes to an electric or electronic module and measuring the conductance between the two electrodes, wherein a conductance measurement above a threshold conductance value indicates the presence of a biological molecule target in the sample, whereas a conductance measurement below or at the threshold conductance value indicates the absence of the biological molecule target in the sample (see page 10, lines 7-23 and page 10, line 24 – page 11, line 5, where the resistance measurements conducted with an ohmmeter provide an indirect measure of the conductance, which is reciprocal ohms; see also page 17, line 33 - page 18, line 8, and page 23 for additional details of the resistance measurements conducted by Mroczkowski).

Mroczkowski also does not teach non-specific deposition of the nucleation center forming entities onto the target. Mroczkowski also does not teach that the method comprises contacting the assay device with a reagent solution comprising monomers of a conductive polymer, which are capable of binding to the nucleation center forming entities and which are

polymerized to form a conductive polymer that bridges the gap between the two electrodes in the assay set.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see abstract, Figure 4, Figure 22, column 2, lines 25-52, column 4, lines 21-25, column 4, lines 41-45, and Table III at column 18). The system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37, column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22). Hollis teaches that the detection of nucleic acid targets can be used in applications such as "genetic research, genetic and infectious disease diagnosis, toxicology testing, individual identification, agriculture identification and breed optimization, quality assurance through contaminant detection, and occupational hazard screening via mutation detection (column 16, lines 35-42)." Also, in the embodiments comprising nucleic acid detection, Hollis teaches that the recognition moiety is a complementary oligonucleotide (see Table III at column 18). In Table III at column 18, Hollis also teaches the use of biotin-avidin interactions to detect targets of interest.

Hollis does not teach non-specific binding of nucleation center forming entities to a target molecule, such as a nucleic acid, or the addition of a reagent solution comprising monomers of a conductive polymer as required by the instant claims.

Olsen teaches that streptavidin may be conjugated to colloidal gold to permit detection of biotin-labeled targets of interest in a sample (column 4, lines 42-67). Olsen also teaches that the disclosed streptavidin-conjugated gold particles may be used in an assay comprising specific capture of a biotin-labeled target of interest using an immobilized recognition moiety followed by detection of the resulting complexes using the streptavidin-conjugated gold particles (column 2, lines 32-61 and column 3, lines 48-62).

Olsen does not teach the use of a reagent solution comprising monomers of a conductive polymer as required by the instant claims.

Engelhardt teaches detecting nucleic acid complexes resulting from hybridization by binding streptavidin to biotinylated nucleotides incorporated via polymerase or terminal transferase activity (column 3, lines 15-24, column 5, lines 60-68, column 6, lines 1-21, column 9, lines 27-43, column 19, lines 20-35, and column 25, lines 41-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Hollis and Olsen with those of Mroczkowski. An ordinary artisan would have been motivated by the teachings of Hollis to adapt the systems, devices, and methods of Mroczkowski to the detection of any biological target, such as nucleic acids, in order to maximize the number of useful applications of the method. Since Hollis taught that nucleic acid detection could be used in numerous useful applications (column 16, lines 35-42 and column 19, lines 5-15), an ordinary artisan would have been motivated to adapt the method of

Mroczkowski to the detection of these useful biological targets in order to further increase the number of useful applications. An ordinary artisan would have had a reasonable expectation of success in doing so, since Mroczkowski taught that the method was not limited to any particular target, and Hollis taught that nucleic acids were suitable targets for electrical detection.

It also would have been prima facie obvious for the ordinary artisan practicing the methods suggested by the combined teachings of Mroczkowski and Hollis to label the target nucleic acids with biotin as taught by either Olsen or Engelhardt to permit detection with streptavidin-conjugated gold particles as taught by Olsen. Since Olsen and Engelhardt taught that nucleic acids could be labeled with biotin to permit non-specific detection with labeled streptavidin, the ordinary artisan would have recognized that non-specific detection via biotin-streptavidin would reduce the cost associated with practicing the methods of Mroczkowski. The ordinary artisan also would have recognized from the teachings of Engelhardt that polymerase-mediated incorporation of biotinylated nucleotides would improve the method resulting from the combined teachings of Mroczkowski, Hollis, and Olsen by providing additional specificity. The ordinary artisan would have had a reasonable expectation of success in combining the teachings of the cited references, since Olsen taught that streptavidin-conjugated gold particles could be used to detect virtually any biotinylated target of interest in a sandwich assay (see above). Thus, the method of claims 26, 28, and 48 are prima facie obvious in view of the combined teachings of the cited references.

13. Claim 35 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300; cited previously) in view of Olsen (US 5,614,832; cited previously).

Claim 35 is drawn to an electronic device for detecting a target biological molecule, and claim 41 is drawn to a method for detecting the presence or absence of at least one target biological molecule using the device of claim 35.

Regarding claim 35, Mroczkowski teaches an electronic device for determining the presence or absence of one or more targets in a sample that comprises an integrated circuit having a first group of N1 conductors and a second group of N2 conductors, defining between them N1xN2 junctions, each junction being formed with an electronic module comprising two electrodes, wherein each electrode is linked to or defined as an integral portion of one of the conductors and supported by a common substrate, and wherein a current flowing between an N1 conductor and an N2 conductor defines a single junction point between the two conductors (see Figure 8 and the accompanying description at page 17, lines 4-32). In the electronic device of Mroczkowski, each pair of electrodes forms part of an assay set that comprises a recognition moiety that binds to a component of a cellular target and is immobilized on the substrate between the electrodes (see, for example, page 17, lines 7-12; see also page 5, lines 5-10 and page 10, lines 7-36 for further description of the recognition moieties). The electronic device of Mroczkowski also comprises a means for determining whether the one or more targets is present in the sample as a result of the extent of electric conductance between the two electrodes of each assay set (see page 17, line 33 – page 18, line 8, where the ohmmeter provides via the obtained resistance measurements an indirect measure of conductance, which is reciprocal ohms).

Finally, the assay sets in the device of Mroczkowski are adapted to accept reagents formulated to deposit a conductive substance onto a complex formed between a recognition moiety and a component of the cellular target (see pages 10 and 17, as discussed in greater detail above). It is noted that the limitations recited in lines 16-29 of the claim only require the electronic device to be **capable of** accepting the recited reagents and do **not** require the presence of the particular reagents recited in lines 16-29 of the claim to be present in the device. Since the device of Mroczkowski is designed to receive reagents (see page 10, for example), it is inherently adapted to receive the reagents described in lines 16-29 of claim 35.

Regarding claim 41, Mroczkowski teaches a method for detecting the presence or absence of one or more targets in a sample by multiplexing that comprises contacting a sample with the electronic device described above under conditions that permit binding of the one or more targets, if present in the sample, to the recognition moieties and determining the conductance in each assay set (see page 17, line 4 – page 18, line 8; see also page 10, line 7 – page 11, line 4). As noted above, the limitations recited in lines 16-29 of claim 35 only require the electronic device to be **capable of** accepting the recited reagents and do **not** require the presence of the particular reagents recited in claim 35 to be present in the device. Claim 41 also does not require the use of the reagents recited in claim 35. Claim 41 only requires detecting the presence or absence of at least one target biological molecule based on a conductance measurement using the device of claim 35.

Mroczkowski does not teach that the disclosed integrated circuit further includes a diode that permits current flow through the electronic module only in the direction from the N1 conductors to the N2 conductors as required by claim 35.

However, as evidenced by Olsen (see, for example, the abstract, column 1, line 59 – column 2, line 13, Figure 1A, and column 2, lines 25-67), diodes were known in the art to be useful for regulating current flow between two electrodes such that current flow only occurs in a single user-selected direction. Olsen also teaches that the diodes permit the isolation of each circuit in a multi-circuit device from one another (column 2, line 35 – column 3, line 8) and further teaches that the disclosed diodes are useful for regulating voltage (column 3, lines 23-35).

Accordingly, it would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to further incorporate a diode into the integrated circuit taught by Mroczkowski. An ordinary artisan would have been motivated to do so in order to obtain a voltage regulating element and the ability to regulate the current flow between each pair of electrodes in the device of Mroczkowski such that current flow only occurs in a single user-selected direction. An ordinary artisan would have recognized from the teachings of Olsen that incorporation of diodes into the integrated circuits of Mroczkowski would have improved the circuits by electrically isolating each pair of electrodes from one another, and thereby, ensuring that the conductance measurements obtained for each circuit were independent. An ordinary artisan would have had a reasonable expectation of success in modifying the integrated circuit of Mroczkowski to further include a diode, since methods of constructing complex diode-containing circuits were well-established in the art as evidenced by the teachings of Olsen. Thus, the electronic device of claim 35 and the method of claim 41 are prima facie obvious over Mroczkowski in view of Olsen.

14. Claims 36, 53, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300; cited previously) in view of Olsen (US 5,614,832; cited previously) and further in view of Hollis et al. (US 5,653,939; cited previously).

Claim 36 is drawn to the device of claim 35, wherein each of the assay sets in the device has a center that is separated from the center of an adjacent assay device by 100 μm or less. Claims 53 and 60 are drawn to the electronic device of claim 35, wherein the recognition moiety is a nucleic acid and the means for determining the presence of a target in the sample comprises a computer, respectively.

The combined teachings of Mroczkowski and Olsen render obvious the device of claim 35, as discussed above.

Mroczkowski does not teach that the centers of the assay sets contained in the device are separated from the centers of adjacent assay sets by a distance within the range recited in claim 36. Mroczkowski also does not teach that the recognition moiety is a nucleic acid and the means for determining the presence of a target in the sample comprises a computer, as required by claims 53 and 60, respectively.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see abstract, Figure 4, Figure 22, and column 2, lines 25-52). The system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module

configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37, column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22). As discussed above, the combined teachings of Mroczkowski and Hollis render obvious the system of claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65, the devices of claims 54 and 62, and the methods of claims 24 and 47-49.

Regarding claim 36, Hollis teaches that the spacing between the centers of the test sites (i.e., assay sets) in the disclosed device is 4 microns, which lies within the claimed range (see, for example, column 6, lines 10-17).

Regarding claim 53, Hollis teaches that the disclosed system can be used to detect cellular, protein, or nucleic acid targets (see column 4, lines 21-25 and lines 41-45 and Table III at column 18). Hollis teaches that the detection of nucleic acid targets can be used in applications such as "genetic research, genetic and infectious disease diagnosis, toxicology testing, individual identification, agriculture identification and breed optimization, quality assurance through contaminant detection, and occupational hazard screening via mutation detection" (column 16, lines 35-42).

Regarding claim 60, Hollis teaches that "[T]he measurement process can be automated via on-chip microprocessor control to provide a very fast method of accessing each test site in the array" (column 20, lines 14-16).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to apply the teachings of Hollis to the electronic device resulting from the combined

teachings of Mroczkowski and Olsen. An ordinary artisan would have been motivated to select any known center-to-center spacing, such as the 4 micron spacing taught by Hollis, for the assay sets in the electronic device resulting from the combined teachings of Mroczkowski and Olsen, recognizing its suitability for the intended purpose. As noted in MPEP 2144.07, the selection of a known material or method based on its suitability for the intended purpose is prima facie obvious in the absence of unexpected results. In this case, since the devices taught by Mroczkowski and Hollis were directed to the same problem (i.e., array-based electrical detection of biological molecules) and possessed a similar structure, an ordinary artisan would have recognized that the center-to-center spacing taught by Hollis was suitable for use in the device resulting from the combined teachings of Mroczkowski and Olsen, and therefore, would have been motivated to select this known center-to-center spacing distance with a reasonable expectation of success. It is also noted that no evidence of unexpected results has been presented with respect to the spacing of the assay sets. An ordinary artisan also would have been motivated to utilize a nucleic acid as the recognition moiety in the device suggested by the combined teachings of Mroczkowski and Olsen. Since Hollis taught that nucleic acid detection could be used in numerous useful applications (column 16, lines 35-42), an ordinary artisan would have been motivated to adapt the device suggested by the combined teachings of Mroczkowski and Olsen to the detection of these useful biological targets in order to maximize the number of useful applications of the system. An ordinary artisan would have had a reasonable expectation of success in doing so, since Mroczkowski taught that the method was not limited to any particular target, and Hollis taught that cells and nucleic acids were suitable targets for detection using electrical systems. Finally, an ordinary artisan would have been

motivated to incorporate a computer as the means for determining the presence of a target in a sample in the device suggested by the combined teachings of Mroczkowski and Olsen. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Hollis taught that the electrical measurements in a similar device could be conducted using a computer to result in a rapid and automated detection step (column 20, lines 14-16). Thus, the devices of claims 36, 53, and 60 are prima facie obvious over Mroczkowski in view of Olsen and further in view of Hollis.

15. Claims 37, 54, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300; cited previously) in view of Hollis et al. (US 5,653,939; cited previously).

These claims are drawn to an electronic device for detecting a target biological molecule.

Regarding claim 37, Mroczkowski teaches a microelectronic device having a plurality of layers, with a first group of conductors being defined as stripes in a one or more first layers and a second group of conductors being defined as stripes in one or more second layers of the device with each of said second layers being separated from a first layer by a non-conductive substance, and wherein electrodes are formed as open ends of the conductors by openings or cut-outs in a vertical direction through the layers (see Figures 6 and 8 and the accompanying descriptions at page 12, lines 1-33 and page 17, lines 4-32; see also pages 21-22). In the device of Mroczkowski, each pair of electrodes forms part of an assay set, which has a recognition moiety for binding to a component of a cellular target selected from the group consisting of a bacterium, a virus, and a cell (see page 5, lines 6-10 and page 10, lines 7-36). The electronic device of

Mroczkowski also comprises a means for determining whether the one or more targets is present in the sample as a result of the extent of electric conductance between each pair of electrodes in each assay set (see page 17, line 33 – page 18, line 8, where the ohmmeter provides via the obtained resistance measurements an indirect measure of conductance, which is reciprocal ohms). Finally, the assay sets in the device of Mroczkowski are adapted to accept reagents formulated to deposit a conductive substance onto a complex formed between a recognition moiety and a component of the cellular target (see pages 10 and 17, as discussed in greater detail above). It is noted that the limitations recited in lines 13-20 of the claim only require the electronic device to be **capable of** accepting the recited reagents and do **not** require the presence of the particular reagents recited in lines 13-20 of the claim to be present in the device. Since the device of Mroczkowski is designed to receive reagents (see page 10, for example), it is inherently adapted to receive the reagents described in lines 13-20 of claim 37.

Mroczkowski does not teach that the recognition moiety is a nucleic acid and the means for determining the presence of a target in the sample comprises a computer, as required by claims 54 and 62, respectively.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see abstract, Figure 4, Figure 22, and column 2, lines 25-52). The system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module

configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37, column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22).

Regarding claim 54, Hollis teaches that the disclosed system can be used to detect cellular, protein, or nucleic acid targets (see column 4, lines 21-25 and lines 41-45 and Table III at column 18). Hollis teaches that the detection of nucleic acid targets can be used in applications such as "genetic research, genetic and infectious disease diagnosis, toxicology testing, individual identification, agriculture identification and breed optimization, quality assurance through contaminant detection, and occupational hazard screening via mutation detection (column 16, lines 35-42)."

Regarding claim 62, Hollis teaches that "[T]he measurement process can be automated via on-chip microprocessor control to provide a very fast method of accessing each test site in the array (column 20, lines 14-16)."

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to apply the teachings of Hollis to the electronic device of Mroczkowski and utilize a nucleic acid as the recognition moiety in the device of Mroczkowski. Since Hollis taught that nucleic acid detection could be used in numerous useful applications (column 16, lines 35-42), an ordinary artisan would have been motivated to adapt the device of Mroczkowski to the detection of these useful biological targets in order to maximize the number of useful applications of the system. An ordinary artisan would have had a reasonable expectation of

success in doing so, since Mroczkowski taught that the method was not limited to any particular target, and Hollis taught that nucleic acids were suitable targets for detection using electrical systems. An ordinary artisan also would have been motivated to incorporate a computer as the means for determining the presence of a target in a sample in the device of Mroczkowski. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Hollis taught that the electrical measurements in a similar device could be conducted using a computer to result in a rapid and automated detection step (column 20, lines 14-16). Thus, the devices of claims 37, 54, and 62 are prima facie obvious over Mroczkowski in view of Hollis.

16. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS and "Olsen 1" below) and further in view of Hurley et al. (Methods in Enzymology (1990) 184: 429-433; newly cited) and further in view of Olsen (US 5,614,832; cited previously and "Olsen 2" below).

Claim 38 is drawn to the system of claim 18 and further limits the structure of the device.

As discussed above, the combined teachings of Mroczkowski, Hollis, Olsen 1, and Hurley render obvious the system of claim 18.

Regarding claim 38, Mroczkowski teaches an electronic device for determining the presence or absence of one or more targets in a sample that comprises an integrated circuit having a first group of N1 conductors and a second group of N2 conductors, defining between them N1xN2 junctions, each junction being formed with an electronic module comprising two electrodes, wherein each electrode is linked to or defined as an integral portion of one of the

conductors and supported by a common substrate, and wherein a current flowing between an N1 conductor and an N2 conductor defines a single junction point between the two conductors (see Figure 8 and the accompanying description at page 17, lines 4-32). Mroczkowski also teaches using the disclosed electronic device to detect the presence or absence of one or more targets in a sample (see page 17, line 4 – page 18, line 8; see also page 10, line 7 – page 11, line 4).

The combined teachings of Mroczkowski, Hollis, Olsen 1, and Hurley do not teach that the disclosed electronic device further includes a diode as required by claim 38.

However, as evidenced by Olsen 2 (see, for example, the abstract, column 1, line 59 – column 2, line 13, Figure 1A, and column 2, lines 25-67), diodes were known in the art to be useful for regulating current flow between two electrodes such that current flow only occurs in a single user-selected direction. Olsen 2 also teaches that the diodes permit the isolation of each circuit in a multi-circuit device from one another (column 2, line 35 – column 3, line 8) and further teaches that the disclosed diodes are useful for regulating voltage (column 3, lines 23-35).

Accordingly, it would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to further incorporate a diode into the integrated circuit taught by Mroczkowski. An ordinary artisan would have been motivated to do so in order to obtain a voltage regulating element and the ability to regulate the current flow between each pair of electrodes in the device of Mroczkowski such that current flow only occurs in a single user-selected direction. An ordinary artisan would have recognized from the teachings of Olsen 2 that incorporation of diodes into the integrated circuits of Mroczkowski would have improved the circuits by electrically isolating each pair of electrodes from one another, and thereby, ensuring that the conductance measurements obtained for each circuit were independent. An ordinary

artisan would have had a reasonable expectation of success in modifying the integrated circuit of Mroczkowski to further include a diode, since methods of constructing complex diode-containing circuits were well-established in the art as evidenced by the teachings of Olsen 2. Thus, the system of claim 38 is prima facie obvious in view of the combined teachings of the cited references.

17. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS and "Olsen 1" below) and further in view of Olsen (US 5,614,832; cited previously and "Olsen 2" below).

Claim 39 is drawn to the method of claim 24 and further limits the structure of the device.

As discussed above, the combined teachings of Mroczkowski, Hollis, and Olsen 1 render obvious the method of claim 24.

Regarding claim 39, Mroczkowski teaches an electronic device for determining the presence or absence of one or more targets in a sample that comprises an integrated circuit having a first group of N1 conductors and a second group of N2 conductors, defining between them N1xN2 junctions, each junction being formed with an electronic module comprising two electrodes, wherein each electrode is linked to or defined as an integral portion of one of the conductors and supported by a common substrate, and wherein a current flowing between an N1 conductor and an N2 conductor defines a single junction point between the two conductors (see Figure 8 and the accompanying description at page 17, lines 4-32). Mroczkowski also teaches

using the disclosed electronic device to detect the presence or absence of one or more targets in a sample (see page 17, line 4 – page 18, line 8; see also page 10, line 7 – page 11, line 4).

The combined teachings of Mroczkowski, Hollis, Olsen 1, and Hurley do not teach that the disclosed electronic device further includes a diode as required by claim 38.

However, as evidenced by Olsen 2 (see, for example, the abstract, column 1, line 59 – column 2, line 13, Figure 1A, and column 2, lines 25-67), diodes were known in the art to be useful for regulating current flow between two electrodes such that current flow only occurs in a single user-selected direction. Olsen 2 also teaches that the diodes permit the isolation of each circuit in a multi-circuit device from one another (column 2, line 35 – column 3, line 8) and further teaches that the disclosed diodes are useful for regulating voltage (column 3, lines 23-35).

Accordingly, it would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to further incorporate a diode into the integrated circuit taught by Mroczkowski. An ordinary artisan would have been motivated to do so in order to obtain a voltage regulating element and the ability to regulate the current flow between each pair of electrodes in the device of Mroczkowski such that current flow only occurs in a single user-selected direction. An ordinary artisan would have recognized from the teachings of Olsen 2 that incorporation of diodes into the integrated circuits of Mroczkowski would have improved the circuits by electrically isolating each pair of electrodes from one another, and thereby, ensuring that the conductance measurements obtained for each circuit were independent. An ordinary artisan would have had a reasonable expectation of success in modifying the integrated circuit of Mroczkowski to further include a diode, since methods of constructing complex diode-containing circuits were well-established in the art as evidenced by the teachings of Olsen 2.

Thus, the method of claim 39 is prima facie obvious in view of the combined teachings of the cited references.

18. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS) and further in view of Hurley et al. (Methods in Enzymology (1990) 184: 429-433; newly cited).

The combined teachings of Mroczkowski and Olsen render obvious the method of claim 25, but they do not teach detection of cellular targets as required by claim 50.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see abstract, Figure 4, Figure 22, and column 2, lines 25-52). The system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37, column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22). Hollis also teaches that the target biological molecule detected using the disclosed system and methods may be a cell, protein, or nucleic acid (see column 4,

lines 21-25 and lines 41-45 and Table III at column 18). In the embodiments comprising cell detection, Hollis teaches that the recognition moiety is a molecule, such as a protein or antibody that binds to a component of the cell (see, for example, Table III at column 18). In Table III at column 18, Hollis also teaches the use of biotin-avidin interactions to detect targets of interest.

Hollis does not teach non-specific binding of nucleation center forming entities to a target selected from a bacterium, a virus, or a cell as required by the instant claims.

Hurley teaches that cells can be labeled with biotin to permit subsequent detection with a labeled streptavidin molecule (pages 429-430). Hurley teaches that the use of the biotin-streptavidin system eliminates the need to design specific antibodies for different cell surface proteins (page 429).

Hurley does not teach labeling the streptavidin with a nucleation center forming entity.

Olsen teaches that streptavidin may be conjugated to colloidal gold to permit detection of biotin-labeled targets of interest in a sample (column 4, lines 42-67). Olsen also teaches that the disclosed streptavidin-conjugated gold particles may be used in an assay comprising specific capture of a biotin-labeled target of interest using an immobilized recognition moiety followed by detection of the resulting complexes using the streptavidin-conjugated gold particles (column 2, lines 32-61 and column 3, lines 48-62).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Hollis, Olsen, and Hurley with those of Mroczkowski. An ordinary artisan would have been motivated by the teachings of Hollis to adapt the systems, devices, and methods of Mroczkowski to the detection of any biological target, such as cells, in order to maximize the number of useful applications of the technology. Since Hollis taught that

nucleic acid detection and cell detection could be used in numerous useful applications (column 16, lines 35-42 and column 19, lines 5-15), an ordinary artisan would have been motivated to adapt the device of Mroczkowski to the detection of these useful biological targets in order to further increase the number of useful applications of the system. An ordinary artisan would have had a reasonable expectation of success in doing so, since Mroczkowski taught that the method was not limited to any particular target, and since Hollis taught that cells were suitable targets for detection via electrical methods.

It also would have been obvious for the ordinary artisan practicing the methods suggested by the combined teachings of Mroczkowski and Hollis to label the target cells with biotin as taught by Hurley to permit detection with streptavidin-conjugated gold particles as taught by Olsen. Since Hurley taught that cells could be labeled with biotin to permit non-specific detection with labeled streptavidin and avoid the need for specific labeled antibodies (e.g., the labeled antibodies described by Mroczkowski), the ordinary artisan would have recognized that non-specific detection via biotin-streptavidin would reduce the cost associated with practicing the methods of Mroczkowski. The ordinary artisan would have had a reasonable expectation of success in doing so, since Hurley taught that the biotin-labeling step did not inhibit binding of the cell surface proteins to antibodies (page 433), and Olsen taught that streptavidin-conjugated gold particles could be used to detect virtually any biotinylated target of interest in a sandwich assay (see above). Thus, the method of claim 50 is prima facie obvious in view of the combined teachings of the cited references.

19. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Olsen et al. (US 5,556,756; cited on an IDS) and further in view of Hurley et al. (Methods in Enzymology (1990) 184: 429-433; newly cited) and further in view of Althainz et al. (Sensors and Actuators B (1996) 33(1-3): 72-76; cited previously).

The combined teachings of Mroczkowski, Olsen, Hurley, and Hollis render obvious the system of claim 1, but they do not teach that the system includes a scanner for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner as required by claim 56.

However, as evidenced by Althainz (see pages 72-73), scanners were known in the art to be useful as part of a means for indirectly measuring conductance at each site in a microsensor array comprising a plurality of electrodes via the measurement of resistance.

Accordingly, it would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate a scanner in the system resulting from the combined teachings of Mroczkowski, Hurley, Olsen, and Hollis as part of the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device. As noted in MPEP 2144.07, it is prima facie obvious to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this case, as evidenced by the teachings of Althainz, a scanner was known in the art to be suitable for use as a component of in a means for obtaining array-based conductance measurements. Also, no evidence of unexpected results with respect to the use of a scanner has been presented. Accordingly, an ordinary artisan would have been motivated to select this

known element for incorporation in the system resulting from the combined teachings of Mroczkowski, Olsen, Hurley and Hollis with a reasonable expectation of success. Thus, the system of claim 56 is prima facie obvious in view of the combined teachings of the cited references.

20. Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Olsen (US 5,614,832; cited previously) and further in view of Althainz et al. (Sensors and Actuators B (1996) 33(1-3): 72-76; cited previously).

The combined teachings of Mroczkowski and Olsen render obvious the device of claim 35 and the method of claim 41, but they do not teach that the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner as required by claim 61.

However, as evidenced by Althainz (see pages 72-73), scanners were known in the art to be useful as part of a means for indirectly measuring conductance at each site in a microsensor array comprising a plurality of electrodes via the measurement of resistance.

Accordingly, it would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate a scanner in the device resulting from the combined teachings of Mroczkowski and Olsen as part of the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device. As noted in MPEP 2144.07, it is prima facie obvious to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this

case, as evidenced by the teachings of Althainz, a scanner was known in the art to be suitable for use as a component of a means for obtaining array-based conductance measurements. Also, no evidence of unexpected results with respect to the use of a scanner has been presented. Accordingly, an ordinary artisan would have been motivated to select this known element for incorporation in the device resulting from the combined teachings of Mroczkowski and Olsen with a reasonable expectation of success. Thus, the device of claim 61 is prima facie obvious in view of the combined teachings of the cited references.

21. Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Althainz et al. (Sensors and Actuators B (1996) 33(1-3): 72-76; cited previously).

The combined teachings of Mroczkowski and Hollis render obvious the device of claim 37, but they do not teach that the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner as required by claim 63.

However, as evidenced by Althainz (see pages 72-73), scanners were known in the art to be useful as part of a means for indirectly measuring conductance at each site in a microsensor array comprising a plurality of electrodes via the measurement of resistance.

Accordingly, it would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate a scanner in the device suggested by the combined teachings of Mroczkowski and Hollis as part of the means for determining the presence of a target in a

sample based on the extent of conductance between each pair of electrodes in the assay device. As noted in MPEP 2144.07, it is prima facie obvious to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this case, as evidenced by the teachings of Althainz, a scanner was known in the art to be suitable for use as a component of a means for obtaining array-based conductance measurements. Also, no evidence of unexpected results with respect to the use of a scanner has been presented. Accordingly, an ordinary artisan would have been motivated to select this known element for incorporation in the device suggested by the combined teachings of Mroczkowski and Hollis with a reasonable expectation of success. Thus, the device of claim 63 is prima facie obvious in view of the combined teachings of the cited references.

Double Patenting

22. The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 24, 25, and 47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-26 of U.S. Patent No. 7,364,920 in view of Olsen et al. (US 5,556,756; cited on an IDS).

The instant claims are drawn to methods for electrically detecting a target analyte, specifically a nucleic acid. The methods comprise binding the target nucleic acid to a complementary oligonucleotide that is immobilized on a substrate between two electrodes, binding a nucleation center-forming moiety non-specifically to the target nucleic acid, depositing metal ions on the nucleation center-forming entities to form a conductive bridge between the electrodes, and detecting the target nucleic acid based on a change in electrical conductance observed upon analyte binding and conductive bridge formation.

Claims 18-26 of the '920 patent teach all of the limitations contained in these claims with the exception of the requirement in the instant claims for the nucleation center forming entities to bind non-specifically to the target nucleic acid.

Olsen teaches that streptavidin may be conjugated to colloidal gold to permit detection of biotin-labeled targets of interest in a sample, such as nucleic acids (column 4, lines 42-67). Olsen also teaches that the disclosed streptavidin-conjugated gold particles may be used in an assay comprising specific capture of a biotin-labeled target of interest, such as a nucleic acid, using an immobilized recognition moiety, such as an oligonucleotide, followed by detection of the resulting complexes using the streptavidin-conjugated gold particles (column 2, lines 32-61 and column 3, lines 48-62).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Olsen with those of the claims of the '920 patent. An

ordinary artisan would have been motivated to label the target nucleic acid with biotin as taught by Olsen to permit detection with streptavidin-conjugated gold particles as taught by Olsen. Since Olsen taught that nucleic acids or proteins could be labeled with biotin to permit non-specific detection with labeled streptavidin, the ordinary artisan would have recognized that non-specific detection via biotin-streptavidin would reduce the cost associated with practicing the methods recited in claims 18-26 of the '920 patent. The ordinary artisan would have had a reasonable expectation of success in doing so, since Olsen taught that streptavidin-conjugated gold particles could be used to detect virtually any biotinylated target of interest in a sandwich assay similar to the assay recited in the claims of the '920 patent. Thus, the instant claims 24, 25, and 47 are not patentably distinct from claims 18-26 of the '920 patent in view of Olsen.

24. Claims 24, 25, and 47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of US Patent No. 7,851,149. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the claims of the '149 patent anticipate the methods recited in the instant claims 24, 25, and 47.

The instant claims are drawn to methods for electrically detecting a target analyte, specifically a nucleic acid. The methods comprise binding the target nucleic acid to a complementary oligonucleotide that is immobilized on a substrate between two electrodes, binding a nucleation center-forming moiety non-specifically to the target nucleic acid, depositing metal ions on the nucleation center-forming entities to form a conductive bridge between the electrodes, and detecting the target nucleic acid based on a change in electrical conductance observed upon analyte binding and conductive bridge formation.

Claims 1-18 of the '149 patent teach all of the limitations contained in these claims, since they recite a method that comprises contacting a nucleic acid-containing sample with an oligonucleotide immobilized on a substrate between two electrodes, binding nucleation center-forming entities non-specifically to the target, forming a conductive bridge between the two electrodes by depositing metal ions on the nucleation center-forming entities in the presence of a reducing agent, and detecting the sample based on an observed change in the current-potential relationship between the two electrodes, which provides a measure of the conductance between the two electrodes. The claims of the '149 patent further teach that the metal ions (i.e., the gold providing agent of claim 1) in the presence of the reducing agent are metastable such that gold deposition on the substrate only occurs in the presence of nucleation center-forming entities (claim 1). Accordingly, claims 1-18 of the '149 patent anticipate the instant claims 24, 25, and 47.

Response to Arguments

25. Applicant's arguments filed on July 12, 2010 have been fully considered and were persuasive in part.

Objection to the Oath/Declaration, Specification, and Drawings

Applicant's arguments, see pages 25-26, have been fully considered and are persuasive. As noted by Applicant, the amendment has obviated the previously made objections, and, therefore, they have been withdrawn.

Objection to claims 1, 20, 22, 23, 25, 26, 28, 35, 37-39, 43, and 44

Applicant argues that the claim amendments have obviated the previously made objections (pages 26-27). This argument was persuasive, and, accordingly, the objections have been withdrawn.

Rejection of claims 25, 26, 28, 37, 50, and 51 under 35 U.S.C. 102(b) as being anticipated by Mroczkowski

Applicant argues that the rejection has been obviated by the claim amendments, which require the nucleation center-forming entities to non-specifically bind to biological molecule targets, since the antibodies disclosed by Mroczkowski bind specifically to their biological molecule targets (pages 27-28). This argument was persuasive, and, accordingly, the previously made rejection has been withdrawn.

Rejection of claims 1, 4-7, 18-20, 22-24, 43, 44, 47-49, 54, 55, 57, 62, and 65 under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski in view of Hollis

Applicant first argues that the rejection has been obviated by the amendment, which requires non-specific binding of the nucleation center-forming entity to the target (page 28). This argument was persuasive, and, accordingly, the rejection has been withdrawn.

Applicant also argues that Hollis teaches away from the claimed method by teaching that limiting the spacing between electrode pairs improves sensitivity (pages 28-29). This argument applies to the new rejections set forth above. Applicant's argument regarding teaching away in Hollis was not persuasive, because Hollis does not actively discourage or discredit other methods for enhancing sensitivity, such as non-specific deposition of nucleation center-forming entities as suggested by the teachings of Hurley and Olsen. As noted in MPEP 2145, for a reference to teach away, it must actively discourage or disparage the claimed solution.

Rejections of claims 8, 9, 35, 36, 38, 39, 41, 53, 56, 60, 61, & 63 under 35 U.S.C. 103(a)

Applicant first argues that the teachings of the secondary references do not remedy the deficiencies of the primary reference or primary combination of references with respect to the independent claims (pages 29-34). This argument is moot in view of the new rejections set forth above, which address the deficiencies in the primary reference or primary combination of references with respect to non-specific deposition of nucleation center-forming entities.

Applicant also argues that Houthoff teaches away from the claimed invention by disclosing platinum or gold, respectively, conjugated to biological molecules, such as proteins or nucleic acids, which would not result in non-specific deposition of the nucleation center forming entities as required by the instant claims (pages 29-30).

This argument was not persuasive, because the teachings of the newly cited Olsen reference suggest non-specific deposition of nucleation center forming entities. Also, Houthoff does not teach away from the claimed invention as argued by Applicant, because the reference does not discourage or disparage non-specific detection methods, such as those suggested by Olsen. As noted in MPEP 2145, active discouragement or disparagement is required for a reference to be considered to teach away. Houthoff is only relied upon to establish that colloidal platinum is an art-recognized equivalent of colloidal gold.

Applicant also argues that Olsen, which was cited in the rejection of claims 35 and 41 under 35 U.S.C. 103(a), teaches away from the claimed invention by teaching specific binding rather than non-specific binding as required by the claims (pages 31-32).

As an initial matter, it is noted that the Olsen reference cited in the previous office action is not the same reference discussed by Applicant at pages 31-32. The previously cited Olsen reference (US 5,614,832) was cited for its teachings with respect to the inclusion of a diode in the claimed devices, and, as such, it does not contain any discussion of gold particles. It would appear that Applicant is referring to the Olsen reference newly applied in this office action (US 5,556,756). Applicant's arguments regarding the newly cited Olsen reference have been fully considered, but they were not persuasive, because, based on the teachings of the instant specification (see, for example, page 6), the biotin-avidin interactions described by Olsen are "non-specific" as required by the claims. Therefore, the reference does not teach away from the claimed invention as argued by Applicant.

Obviousness-Type Double Patenting Rejections of claims 1, 4-9, 18-20, 22-26, 28, 43, 44, 47-51, 55-57, and 65 citing US 7,364,920

Applicant argues that the rejection is improper, because the filing date of the '920 patent is later than the filing date of the instant application (pages 34-35).

Upon further consideration and in view of the claim amendments, claims 24, 25, and 47 are currently rejected on the ground of non-statutory obviousness-type double patenting based on US 7,364,920 and Olsen (US 5,556,756).

Applicant's argument regarding the propriety of the double patenting rejection was not persuasive, because, as noted in MPEP 804.02 VI, "37 CFR 1.321(c)(3) requires that a terminal disclaimer filed to obviate a non-statutory double patenting rejection based on commonly owned conflicting claims include a provision that any patent granted on that application be enforceable only for and during the period that the patent is commonly owned with the application or patent

which formed the basis for the rejection. 37 CFR 1.321(d) sets forth the requirements for a terminal disclaimer where the claimed invention resulted from activities undertaken within the scope of a joint research agreement. These requirements serve to avoid the potential for harassment of an accused infringer by multiple parties with patents covering the same patentable invention. See, e.g., In re Van Ornum, 686 F.2d 937, 944-48, 214 USPQ 761, 767-70 (CCPA 1982)." Also, in view of possible patent term adjustments to any patent issuing from the instant application, it cannot currently be determined that the instant application will necessarily expire before the '920 patent (MPEP 804.02 VI).

Provisional Obviousness-Type Double Patenting Rejections of claims 1, 4-9, 18-20, 22-26, 28, 43, 44, 47-51, 55-57, and 65, citing Application Serial No. 10/638,503

Since the last office action, the '503 application has issued as US Patent No. 7,851,149.

Upon further consideration, in view of the issuance of the '503 application as US Patent No. 7,851,149, and in view of the claim amendments, claims 24, 25, and 47 are currently rejected on the ground of non-statutory obviousness-type double patenting based on US 7,851,149.

Applicant argues that the rejections are improper, because the filing date of the '530 application is later than the filing date of the instant application (pages 35-36).

Applicant's argument was not persuasive, because, as noted in MPEP 804.02 VI, "37 CFR 1.321(c)(3) requires that a terminal disclaimer filed to obviate a non-statutory double patenting rejection based on commonly owned conflicting claims include a provision that any patent granted on that application be enforceable only for and during the period that the patent is commonly owned with the application or patent which formed the basis for the rejection. 37

CFR 1.321(d) sets forth the requirements for a terminal disclaimer where the claimed invention resulted from activities undertaken within the scope of a joint research agreement. These requirements serve to avoid the potential for harassment of an accused infringer by multiple parties with patents covering the same patentable invention. See, e.g., In re Van Ornum, 686 F.2d 937, 944-48, 214 USPQ 761, 767-70 (CCPA 1982)." Also, in view of possible patent term adjustments to any patent issuing from the instant application, it cannot currently be determined that the instant application will necessarily expire before the '920 patent (MPEP 804.02 VI).

Conclusion

26. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637